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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,824	09/08/2003	Stephen I. Rennard	UNMC/03017/0008	7805

7590 01/03/2007  
Moser, Patterson & Sheridan, LLP  
Suite 1500  
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EXAMINER
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AFREMOVA, VERA

ART UNIT	PAPER NUMBER
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1657

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/03/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/658,824	RENNARD ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 25 September 2006 and 23 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 11-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 11-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/23/2006</u>  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/25/2006 has been entered.

Claims 11-19 as amended and new claims 20-22 (9/25/2006) are pending and under examination.

### ***Information Disclosure Statement***

The missing copy of the reference by Morstyn (IDS filed 1/04/2004 and IDS filed 10/23/2006) was not provided. The IDS form 1449 does not indicate the pages or portion of the reference by Morstyn that caused it to be listed. Therefore, the information disclosure statement filed 1/05/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered in full.

### ***Claim Rejections - 35 USC § 112***

Claims 11-19 as amended and new claims 20-22 remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 as amended is indefinite and unclear about what condition contributes or induces differentiation as intended. Claim confusingly recites “inducing differentiation” by growing EB in the cell culture medium without “reliance on composition of the cell culture medium”. The claimed non-reliance on the composition of the cell culture medium is particularly unclear since the claims 12-14 are drawn to addition of cytokines that induce differentiation as intended and as disclosed by applicants (par. 0033 and 0057).

Claim 11 as amended remains indefinite by recitation of “substantially homogenous populations” of fibroblasts in the lack of definitions about how much and/or what % is intended for the claimed term “substantially homogenous populations”.

### ***Claim Rejections - 35 USC***

#### ***New matter***

Claims 11-19 as amended and new claims 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

1. Insertion of the limitation without “differentiation occurs without reliance on composition of the cell culture medium” in claim 11 has no support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly

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limited genus that would show possession of the concept of “without reliance on composition of the cell culture medium” as claimed.

The literal support for the present amendment is lacking in the specification and the specification clearly recite that “various cytokines and growth factors are used to induce differentiation” (par. 0033). The exemplified disclosure demonstrates that addition of FGF induces differentiation of fibroblasts (par. 0057).

Thus, there is no sufficient support of the claimed limitation “differentiation occurs without reliance on composition of the cell culture medium”. This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of “differentiation occurs without reliance on composition of the cell culture medium” is considered to be the insertion of new matter for the above reasons.

2. Insertion of the limitation “produces homogenous population of fibroblasts” in the claims 21 and 22 has no support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus that would show possession of the concept of making or producing the “homogenous population of fibroblasts”.

The literal support for the present amendment is lacking in the specification. The exemplified disclosure demonstrates that addition of growth factors induces more or less extensive differentiation of fibroblasts (par. 0056-0058). This is not a sufficient support for the

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new limitation since term “homogenous” means 100% pure. Nowhere specification recites or demonstrates making a homogenous population of fibroblasts that would be 100% pure.

The instant insertion of new limitation is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of the limitation “produces homogenous population of fibroblasts” in the claims 21 and 22 is considered to be the insertion of new matter for the above reasons.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 11-14 and 19 as amended and new claims 20 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2003/0119107 (Dang et al).

Claims are directed to a method for producing fibroblasts wherein the method comprises step of obtaining embryonic stem (ES) cells, step of culturing ES to form embryoid bodies (EB), step of isolating EB, step of casting EB in a culture medium in 3D scaffolding material that is a gel, step of growing EB in the 3D material thereby inducing differentiation to produce

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fibroblasts. Some claims are further drawn to the use of differentiation-inducing “cytokines” including TGF beta or FGF.

US 2003/0119107 (Dang et al) discloses a method for generation of cells or for producing cells from spheroids or from embryoid bodies wherein the method comprises step of obtaining embryonic stem (ES) cells, step of culturing ES to form embryoid bodies (EB), step of isolating EB, step of casting EB in a culture medium in 3D scaffolding material that is 3% agarose gel and step of growing EB encapsulated into the 3D material in a stirred bioreactor, for example: see abstract, par. 0120, par. 0116. Thus, the cited patent teaches method that comprises identical active steps and identical structural element as required by the claimed method. Therefore, the cited method results in the production of identical cells within the intended meaning of the claimed phrase “thereby inducing differentiation of the embryoid bodies to produce substantially homogenous populations of fibroblasts”.

As applied to the claims 12-14 and 19 the cited document also teaches the use of differentiation-inducing cytokines (par. 0082) including the use of TGF beta or FGF for producing mesodermal cells (table 11) that include and/or would be fibroblasts accordingly applicants’ description (see instant specification page 11. par. 0034, line 7).

Thus, the cited document anticipates the presently claimed invention.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11-19 as amended and new claims 20-22 remain/are rejected under 35 U.S.C.

103(a) as being unpatentable over US 2003/0119107 (Dang et al) taken with Dani et al.

["Differentiation of embryonic stem cells into adipocytes in vitro". Journal of Cell Science (1997), 110: 1279-1285] and US 6,576,464 (Gold et al.).

Claims 11-14, 19 and 20 as explained above. Some claims are further drawn to extraction of differentiated cells from the 3D material by digestion and centrifugation and to culturing the digested cells in monolayer culture. Some claims are further drawn to the use of media with 2% serum at step of inducing differentiation of embryonic cells and with 10% for monolayer culture. Some claims are further drawn to making homogenous population of fibroblasts.

US 2003/0119107 (Dang et al) is relied as explained above for the disclosure of a method for controlled generation of cells from embryonic stem cell-derived embryoid bodies that are encapsulated into 3D scaffold material. US 2003/0119107 teaches that cells are released from the 3D material by digestion (par. 0160). The cited document US 2003/0119107 also teaches the use of differentiation-inducing cytokines (par. 0082) including the use of TGF beta or FGF for producing mesodermal cells (table 11) that include and/or would be fibroblasts accordingly applicants' description (see instant specification page 11. par. 0034, line 7).

The cited document US 2003/0119107 discloses that in most cases differentiation inducing additives and/or factors are added to the serum-containing medium (table 10) and the disclosed protocols of culturing ES and EB encompass the use of 15% and/or 20% serum (par. 010, 0114).



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US 2003/0119107 is lacking particular disclosure about the use of 2% and 10% serum containing media.

However, the cited reference by Dani et al. discloses the use of 10% serum in differentiation media in the method for culturing and differentiating embryonic cells, formation of embryoid bodies (page 1280, col. 1, par. 3) and production fibroblast-like cells (page 1280 col. 2, par. 1, lines 17-18).

Further, US 6,576,464 teaches that differentiation of embryonic cells can be induced by withdrawal of serum or by substituting medium devoid of serum at the time of replating (col.16, lines 53-56). Thus, reduction of serum content in the medium intended for induction of differentiation would be an obvious protocol to ordinary skill practitioner at the time the claimed invention was made. One of skill in the art would have been motivated to reduce amount of serum for the expected benefits in inducing differentiation of embryonic cells as suggested by US 6,576,464. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

### ***Response to Arguments***

Applicant's arguments filed 9/25/2006 have been fully considered but they are not persuasive.

With regard to the issues under 112-2 applicants argue that the phrase "substantially homogenous populations" of fibroblasts would be clear to one of skilled in the art even in the

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lack of specific amounts or particular % as intended for the claimed term "substantially homogenous populations". Applicants appear to argue that this phrase would mean less than 100% pure but not a mixed population. Yet, less than 100% might be zero and, clearly, less than 100% pure cell population would be at the very least a mixed population.

With regard to the claim rejection under 35 U.S.C. 102(e) as being anticipated by US 2003/0119107 (Dang et al) Applicants appear to argue (response page 6) that Dang et al. teach away by stating that the matrix "does not interfere with the growth and differentiation of EBs" (par. 160) and that the matrix does not "influence differentiation or growth of EBs in any manner" (paragraph 168). Upon review this argument does not appear to have any persuasive grounds with respect to the claimed invention. The statements cited by applicants actually mean that matrix does not negatively affect or interfere with development of EB as it would naturally occur. The cited document teaches that matrix prevents from uncontrolled aggregation rather from development and differentiation as it appears to be argued by applicants.

With regard to claim rejection under 35 USC § 103 applicants argue that there is no suggestion to combine references. However, the cited references are in the same field of endeavor (such as method of culturing and differentiation ES and EB in matrix) and they seek to solve the same problems as the instant application and claims (such as production of fibroblasts like cells), and one of skill in the art is free to select components available in the prior art, *In re Winslow*, 151 USPQ 48 (CCPA, 1966).

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

December 22, 2006



VERA AFREMOVA

PRIMARY EXAMINER